REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Kindly clarify the status of the pending claims.

In item 4 on page 1 of the Office Action, claims 1-13, 17, 20, 26-30, 35 and 36 were incorrectly listed as pending. Instead, claims 1-17 and 19-36 were pending.

Claims 14-16, 19, 21-25 and 31-34 are withdrawn.

Claims 1-13, 17, 20, 26-30 and 35-36 have been examined on the merits and stand rejected.

Claims 1 and 5-12 have been amended.

Claim 1 is amended to incorporate the limitations of original claims 3-4.

Claims 5-12 are amended to depend on claim 1 due to the cancellation of claim 3.

Claims 2-4 and 36 are canceled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any canceled subject matter.

Therefore, no new matter has been added by this amendment.

Claims 1, 5-17 and 19-35 are now pending in this application.

II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-13 and 17 remain rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The basis for this rejection is that claims 1 and 17 recite "non-carbamate." However, the rejection points out that other variables still have "carbamoyl" as a substitutent, which is allegedly inconsistent with the recitation "non-carbamate amine compound." See item 1 on page 2 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims for the following reasons.

Generally, a carbamate compound, which is an ester of carbamic acid, is a compound having the group $-NHCO_2R$, wherein R is a hydrocarbon group. Accordingly, compounds having carbamoyl ($-CONH_2$), mono-loweralkyl-carbamoyl ($-CONHR^x$, wherein R^x is a lower

alkyl) or di-loweralkyl-carbamoyl ($CONHR^xR^y$, wherein R^x and R^y are a lower alkyl) do not belong to carbamate, unless such groups are linked to an oxygen atom.

For the Examiner's convenience, attached herewith are copies of the corresponding page of the Japanese Edition of Stedman's Medical Dictionary (published by Williams & Wilkins, Baltimore, Maryland, U.S.A.) in which the definition of carbamate and carbamoyl is described. Also, and an English online versions of Stedman's Medical Dictionary. The dictionary definitions therein support the definitions described above and the position taken below.

Applicants submit that the carbamoyl, mono-loweralkyl-carbamoyl and di-loweralkyl-carbamoyl in the claims of the present invention are not linked directly to an oxygen atom. Thus, the compound having a carbamate group is not included in the scope of the compound of the present invention. As such, the claims are consistent with the recitation "non-carbamate amine compound" of claim 1.

In view of the above, the rejection of claims 1-13 and 17 under 35 U.S.C. § 112, second paragraph, is untenable and should be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 17 remains rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The basis for this rejection is that claim 17 requires a combination therapy of an α-blocker and an non-carbamate amine compound having an acetylcholinesterase-inhibiting action ("AchE inhibitor"). The rejection is premised on the position that without guidance on what proportion of each agent to combine, mixing an α-blocker with an AchE inhibitor could be dangerous due to a potentially fatal decrease in blood pressure. The rejection further states that the state of the art does not yield any teaching for such a mixed composition. The rejection notes that the references previously cited by the Applicants do not support the enablement of claim 17, because they teach the combination of α-blocker with a cholinergic agent and not with AchE inhibitor as claimed. See item 2 pages 2-3 of the Office Action. This rejection is respectfully traversed.

The test of enablement is whether one reasonably skilled in the art could make or use the invention based on the disclosure in the specification coupled with the knowledge in the art without undue experimentation.

First, regarding the safety and efficacy concerns, the mechanism of dysuria caused by prostatomegaly can be classified as: (1) a mechanical urethral obstruction caused by prostatomegaly; and (2) a functional urethral obstruction caused by hypertonia of smooth muscle of prostate. Treatment with anti-androgen and a surgical treatment to shrink the prostate are effective for the former. Therapy to release the tone in prostate and smooth muscle of urethra with a blocker, such as tamsulosin, which decreases urethral resistance is effective for the latter case.

Therefore, for prostatomegaly based on functional urethral obstruction, the combined use of α-blocker blocker and the compound of the present invention can be expected to provide a potent improving action of urination function by decreasing urethral resistance with an α-blocker, and increasing the contraction potency of the muscle of urinary bladder with an AchE inhibitor without fear of high pressure urination. Accordingly, such combination therapy is safe and useful for treating dysuria. In fact, a synergic effect was observed in the improving activity of urination efficiency as shown in Tables 8- 9 of Experimental Example 4 of the specification.

Also, regarding the diagnosis of mechanical urethral obstruction and functional urethral obstruction, the skilled clinician can easily diagnose such by ultrasound imaging, etc. Therefore the concomitant treatment of an α-blocker and a non-carbamate AchE inhibitor does not pose a risk.

Furthermore, not withstanding that the claimed pharmaceutical is effective and safe, it is well established that safety and efficacy should are not to be confused with the requirements of patentability. In this regard, the M.P.E.P. at § 2107.03, V (pages 2100-45 to 2100-46) indicates that "it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness." Similarly, the M.P.E.P. at § 2164.01(c) (pages. 2100-180) states that "[t]he applicant need not demonstrate that the invention is completely safe."

Second, with regard to dosage and administration, the content of the non-carbamate amine compound having AChE inhibitory action and the dosage as a therapeutic agent for urination difficulty in a combined application are described in detail on pages 108-109 of the specification.

In summary, one of skill in the art could make and safely use the claimed pharmaceutical composition comprising a combination of α-blocker and AchE inhibitor without undue experimentation given the guidance in the specification and the knowledge in the art.

Therefore, the rejection of claim 17 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 102

Claims 1-3, 6-9 and 35 remain rejected under 35 U.S.C. § 102(b), as anticipated by Kawakita et al., US 5,864,039. See item 3 on pages 3-4 of the Office Action.

To anticipate a claim, a cited prior art reference must either expressly or inherently teach each and every element of the claimed invention.

The rejected claims have been amended to incorporate the subject matter of non-rejected claim 4. Specifically, Ar of claim 1 has been limited to the tricyclic compounds of claim 4. As such, the amended claims relate to a compound which is distinct and different from the two compounds disclosed in US '039. Since US '039 does not disclose or mention the compound of the amended claims, US '039 cannot be said to teach or suggest each and every element of the claimed invention. For these reasons, it is respectfully submitted that the present amendment overcomes this rejection.

Accordingly, reconsideration and withdrawal of this rejection is respectfully solicited.

V. REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-13, 20 and 35-36 were rejected under 35 U.S.C. § 103(a) as obvious over Gotto et al., US 5,528,800 in view of Tobin et al., Eur. J. Pharm, vol. 281, pp. 1-8 (1995) and Lai et al., Life Sciences, vol. 62, no. 13, pp. 1179-1186 (1998). See item 4 on pages 4-6.

This rejection is respectfully traversed as applied to the amended claims.

Gotto does not disclose or suggest a method for improving execretory potency of urinary bladder. Instead, the Examiner has noted that one of ordinary skill in the art may have been able to contemplate promoting the contraction of bladder muscle by inhibiting AchE based on the teachings of Tobin and Lai. These references disclose the relationship between acetylcholine receptor and contraction potency of bladder.

However, the inhibition of AchE has the possibility of leading to the following two actions, which do not always result in an improvement in urination function.

First, inhibition of AchE may contract the bladder, not only on urination, but also during the urinary storage period (collection of urine). The contraction of the bladder during urinary storage period results in decreasing the compliance of the bladder (an indicator of urinary storage potency of bladder). It also impairs the normal urinary storage function of the bladder, which causes pollakiuria and incontinence of urine.

Second, an AchE inhibitor has the possibility of contracting not only the smooth muscle of the bladder, but also the sphincter muscle of the urethra. The contraction of sphincter muscle of urethra causes a rise in urethral resistance, and does not lead to facilitation in urination function of bladder, rather strains excessively bladder muscle, which results in a high pressure urination.

Moreover, attached are the following documents which provide additional data as to the non-obviousness of the present invention: (1) Document 1 – Increasing activity of the compound of Reference Example 15 on bladder contraction; and (2) Document 2 – Action on urodynamics of the compound of Reference Example 15. The data shown therein clearly points to an unexpected characteristic of the claimed invention over the prior art.

For instance, the carbamate AchE inhibitors, distigmine and neostigmine, both showed a contracting activity to the isolated detrusor muscle in the ground state (see Fig 7 and 8 of Document 1). This further decreased the compliance of the bladder in the urodynamic study using anesthetized guinea pigs.

In contrast to these carbamate AchE inhibitors, the compound of Reference Example 15 of the present invention unexpectedly showed no contracting activity at all to the isolated detrusor muscle in the ground state (see Fig 7 and 8 of Document 1). In addition, the compound did not decrease the compliance of bladder at all in the urodynamic study using anesthetized guinea pigs (see Fig 18 of Document 2). Also, the compound of the present invention had no effect on the ability of urinary storage of the bladder.

Analyzing the results of the urodynamic study in more detail, distigmine and neostigmine raised the urination pressure depending on the dosage, rather than decreasing the maximum flow rate of urine depending on the dose, and did not enhance the urination function. In other words,

an increase in urethral resistance was observed.

On the other hand, the compound of Reference Example 15 of the present invention did not increase the urination pressure when the dosage was increased. The maximum flow rate of urine was increased depending on the dose. Thus, in contrast to the carbamate AchE inhibitor, the compound of Reference Example 15 of the present invention enhanced the excretion potency of bladder without increasing urethral resistance (see Fig 19 of Document 2).

Thus, the present invention is based on the findings that the compounds of the present invention not only have a potent contracting activity for the bladder muscle, but they also unexpectedly act selectively on the bladder on urination without impairing the urinary storage function of bladder, and they do not enhance the urethral resistance, which is different from the carbamate cholinesterase inhibitor of the prior art. Consequently, the compound of the present invention has high urination efficiency, a potent action for improving excretory potency of the urinary bladder and a therapeutic effect for dysuria, not found in the prior art.

Although Gotto discloses that the compound of the present invention has AchE inhibitory activity, Gotto does not disclose the action on bladder muscle, much less the effect on urinary storage function of bladder and the action on urethral resistance.

Even if the cited documents are combined which have no description or teaching about contraction activity for bladder muscle and treating effect of urinary disturbance, the outstanding effects of the present invention (improving activity of excretory potency of urinary bladder and therapeutic action of dysuria) cannot be suggested.

Lastly, claims 26-30 were rejected under 35 U.S.C. § 103(a) as obvious over Gotto et al., US 5,528,800. See item 5 on page 6.

As acknowledged by the Examiner, Gotto does not disclose or suggest the specific crystals of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one of claims 26-30. The Examiner notes that Gotto discloses an analogous crystalline compound. However, even if the compound in Gotto inhibits AchE, this is not motivation to alter the compound in Gotto to arrive at the specific compound claimed. Accordingly, Gotto fails to disclose or suggest each and every element of the claimed invention

and lacks the requisite motivation to modify its teachings to arrive at the claimed invention.

For these reasons, the obviousness rejections are untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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ATTACHMENT TO AMENDMENT AND REPLY:

1. Copy of the page of Stedman's Medical Dictionary containing dictionary definition of carbamate compound including online versions of Stedman's Medical Dictionary for these definitions.

2. Document 1 – Increasing activity of the compound of Reference Example 15 on bladder contraction; and

3. Document 2 – Action on urodynamics of the compound of Reference Example 1

節裏の形成手術).

cap·su·lor·rha·phy (kap-sū-lōr'ă-fē) [L. *capsula*, capsule + *rhaphē*, suture]. 嚢縫合(術), 包縫合(術) (被膜の裂傷の縫合. 特に関節脱臼の再発防止のために関節嚢を縫合すること).

cap·su·lo·tome (kap'sū-lō-tōm). 切嚢刀. = cystotome (2).

cap·su·lot·o·my (kap-sū-lot'ŏ-mē) [L. *capsula*, capsule + G. *tomē*, a cutting]. 嚢切開(術), 包切開(術) 1 (白乳房インプラントの周囲の被膜を切開すること. 例えば, 異物周囲に形成される瘢痕の切開. 2 特に水晶体嚢外摘出術を行う場合の水晶体嚢の切開).

renal c. 腎切開(術) (腎臓の嚢の切開).

cap·to·pril (kap'tō-pril). カプトプリル; 1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (高血圧およびうっ血性心不全の治療に用いるアンギオテンシン変換酵素阻害薬).

cap·ture (kap'chūr) [L. *capio*, pp. *-tus*, to take, seize]. 捕捉, 捕獲 (別の場所で発生した粒子や電気的興奮をつかまえ保持すること).

atrial c. 心房捕捉 (完全房室ブロック, 房室結節性または心室性の異所性収縮または頻脈のような, 無反応休止期の後の逆行性インパルスによる心房調節).

electron c. 電子捕獲 (放射性崩壊の様式. 軌道電子(通常はK殻の電子)が核によって捕獲され, 陽子が中性子に変化し, ニュートリノとガンマ線の放出を伴う. また, K殻に生じた孔に外殻電子が遷移することで, 特性X線も放出される). = K c.

K c. K捕獲. = electron c.

ventricular c. 心室捕捉 (心房または房室接合部に発する電気的興奮を心室が捕捉すること).

Capuron, Joseph, フランスの医師, 1767—1850. →C.'s *points*.

ca·put, gen. **ca·pi·tis,** pl. **ca·pi·ta** (kap'ut, ka'put; kap'i-tis; kap'i-tă) [L.]. 頭, あたま (中[NA]. 動物体の上端または前端にあって, 脳および視・聴・味・嗅などの感覚器を収容している部分. 2 [NA]. 器官その他の構造の上端・前端・大きいほうの端部などで丸く拡大している部分. 3 骨の丸い形をした端部. 4 筋の両端のうちで, その筋が収縮したとき, 付着している骨の動きの少ないほうの端部). = head.

c. angula're quadra'ti la'bii superio'ris 上唇方形筋の口角頭. = levator labii superioris alaeque nasi *muscle*.

c. bre've [NA]. 短頭. = short *head*.

c. breve musculi bicipitis brachii [NA]. = short *head* of biceps brachii muscle.

c. breve musculi bicipitis fem'oris = short *head* of biceps femoris muscle.

c. cor'nus 後角尖. = *apex* of the posterior horn.

c. cos'tae [NA]. 肋骨頭. = *head* of rib.

c. epididymid'is [NA]. 精巣上体頭. = *head* of epididymis.

c. fem'oris 大腿骨頭. = *head* of femur.

c. fib'ulae [NA]. 腓骨頭. = *head* of fibula.

c. gallinaginis (gal-i-naj'i-nis) [Mod. L. snipe's head]. = seminal *colliculus*.

c. humera'le [NA]. 上腕頭. = humeral *head*.

c. humerale musculi flexoris carpi ulnaris [NA]. 尺側手根屈筋の上腕骨頭 (→humeral *head*).

c. humerale musculi pronatoris teretis [NA]. 円回内筋の上腕骨頭 (→humeral *head*).

c. hu'meri [NA]. 上腕骨頭. = *head* of humerus.

c. humeroulna're musculi flexoris digitorum superficialis [NA]. = humeroulnar *head* of flexor digitorum superficialis muscle.

c. infraorbita'le quadra'ti la'bii superio'ris = levator labii superioris *muscle*.

c. latera'le [NA]. 外側頭. = lateral *head*.

c. laterale musculi gastrocnemii [NA]. 腓腹筋の外側頭 (→lateral *head*).

c. laterale musculi tricipitis brachii [NA]. 上腕三頭筋の外側頭 (→lateral *head*).

c. long'um [NA]. 長頭. = long *head*.

c. longum musculi bicipitis brachii [NA]. 上腕二頭筋の長頭 (→long *head*).

c. longum musculi bicipitis fem'oris [NA]. 大腿二頭筋の長頭 (→long *head*).

c. longum musculi tricipitis brachii [NA]. 上腕三頭筋の長頭 (→long *head*).

c. mal'lei [NA]. つち骨頭. = *head* of malleus.

c. mandib'ulae [NA]. 下顎頭. = *head* of mandible.

c. media'le [NA]. 内側頭. = medial *head*.

c. mediale musculi gastrocnemii [NA]. 腓腹筋の内側頭 (→medial *head*).

c. mediale musculi tricipitis brachii [NA]. 上腕三頭筋の内側頭 (→medial *head*).

c. medu'sae [*Medusa*, ギリシア神話上の人物]. メズサの頭 (臍から放射状に出る拡張蛇行静脈. Cruveilhier-Baumgarten 症候群にみられる. 2 虹彩ルベオーシスにおいて, 角膜輪郭を取り巻く怒張した毛様体動脈). = Medusa head.

c. nu'clei cauda'ti [NA]. 尾状核頭. = *head* of the caudate nucleus.

c. obli'quum [NA]. 斜頭. = oblique *head*.

c. obliquum musculi adductoris hallucis [NA]. 足母指内転筋の斜頭 (→oblique *head*).

c. obliquum musculi adductoris pollicis [NA]. 手母指内転筋の斜頭 (→obique *head*).

c. os'sis fem'oris [NA]. 大腿骨頭. = *head* of femur.

c. os'sis metacarpa'lis [NA]. 中手骨頭. = *head* of metacarpal bone.

c. os'sis metatarsa'lis [NA]. 中足骨頭. = *head* of metatarsal bone.

c. pancrea'tis [NA]. 膵頭. = *head* of pancreas.

c. phalan'gis [NA]. (指節骨の)頭. = *head* of phalanx.

c. profun'dum musculi flexoris pollicis brevis [NA]. = deep *head* of flexor pollicis brevis.

c. quadra'tum 四角頭 (頭頂隆起や前頭隆起が肥厚したために生じる大きな四角形をした頭. くる病の小児にみられる).

c. radia'le [NA]. 橈骨頭. = radial *head*.

c. ra'dii [NA]. 橈骨頭. = *head* of radius.

c. sta'pedis [NA]. あぶみ骨頭. = *head* of stapes.

c. succeda'neum 産瘤 (浮腫状の頭腫で, 出生時に新生児の児頭先進部にできる. 滲出液は浮腫からなり, 骨膜上に貯留する. 滲出液が血液からなり, 骨膜下にたまる頭血腫 cephalhematoma とは異なる).

c. superficia'le musculi flexoris pollicis brevis [NA]. = superficial *head* of flexor pollicis brevis muscle.

c. ta'li [NA]. 距骨頭. = *head* of talus.

c. transver'sum [NA]. 横頭. = transverse *head*.

c. transversum musculi adductoris hallucis [NA]. 足母指内転筋の横頭 (→transverse *head*).

c. transversum musculi adductoris pollicis [NA]. 手母指内転筋の横頭 (→transverse *head*).

c. ul'nae [NA]. 尺骨頭. = *head* of ulna.

c. ulna're [NA]. 尺骨頭. = ulnar *head*.

c. ulnare musculi flexoris carpi ulnaris [NA]. 尺側手根屈筋の尺骨頭 (→ulnar *head*).

c. ulnare musculi pronatoris teretis [NA]. 円回内筋の尺骨頭 (→ulnar *head*).

c. zygomat'icum quadra'ti la'bii superio'ris 上唇方形筋の頬骨頭. = zygomaticus minor *muscle*.

Carabelli, Georg (Edler von Lunkaszprie). オーストリアの歯科医, 1787—1842. →*cusp* of C.; C. *tubercle*.

car·a·mel (kar'ă-mel) [Sp. < L. *calamellus* < L. *calamus*, reed]. カラメル (砂糖をアルカリとともに加熱することにより得られる物質の濃縮液. 濃厚な黒褐色の液体. 製剤上, 着色剤および着香料として用いる). = burnt sugar.

ca·ram·i·phen eth·ane·di·sul·fo·nate (ka-ram'i-fen eth'ān-di-sŭl'fō-nāt). エタンジスルホン酸カラミフェン; diethylaminoethyl 1-phenylcyclopentanecarboxylate ethanedisulfonate (鎮咳薬).

ca·ram·i·phen hy·dro·chlo·ride 塩酸カラミフェン; diethylaminoethyl-1-phenylcyclopentane-1-carboxylate hydrochloride (合成鎮痙薬. 脳幹神経節の疾病, 例えば, パーキンソン症候群や肝レンズ核変性症の治療に用いる).

ca·ra·te (kă-rah'tē). カラテ. = pinta.

carb-, carbo- [L. *carbo*, charcoal]. 炭素を含有することを示す接頭語. 特に炭素原子を含む基がついていることを示す接頭語.

car·ba·chol (kar'bă-kol). カルバコール (緑内障の治療において, 眼に局所的に用いる副交感神経興奮薬).

car·ba·dox (kar'bă-doks). カルバドックス; methyl 3-(2-quinoxalinylmethylene)carbazate N^1,N^4-dioxide (抗菌薬).

car·ba·mate (kar'bă-māt). = carbamoate; carbaril. カルバミン酸塩またはエステル. ウレタン催眠薬の基剤となる. 2 有機リン酸塩と類似したコリンエステラーゼを阻害する殺虫薬の一群. カルバリルが最も頻繁に用いられる.

c. kinase カルバメートキナーゼ (カルバモイルリン酸と ADP が ATP, NH_3, CO_2 を生成する反応を触媒するホスホトランスフェラーゼ).

car·bam·az·e·pine (kar-bam-az'ĕ-pēn). カルバマゼピン; 5-*H*-dibenz[*b*,*f*]azepine-5-carboxamide (抗痙攣薬. 三叉神経痛の痛みの緩和にも有効).

car·bam·ic ac·id (kar-bam'ik). カルバミン酸; NH_2-COOH (カルバミン酸塩を生成するといわれる仮説上の酸. アシル基はカルバモイルである).

car·bam·ide (kar'bă-mid). カルバミド (urea を裂す現在では用いられない語).

car·bam·o·yl (kar'bă-mō-il). カルバモイル (1価のアシル基 NH_2-CO- で, その転移はある種の生化学的反応で重要な役割を果たす. 例えば, 尿素サイクルではカルバモイルリン酸を経由する).

car·bam·o·yl·as·par·tate de·hy·drase (kar'bă-mō-il-as-par'tāt). カルバモイルアスパルテートデヒドラーゼ. = dihydro-orotase.

***N*-car·bam·o·yl·as·par·tic** (kar'bă-mō-il-as-par'tik). *N*-カルバモイルアスパラギン酸. = ureidosuccinic acid.

car·bam·o·yl·a·tion (kar-bă-mō-il-ā'shŭn). カルバモイル化 (カルバモイル含有分子(例えばカルバモイルリン酸)からカルバモイル基のアミノ基のようなアクセプター部分への転移).

car·bam·o·yl·car·bam·ic ac·id (kar'bă-mō-il-kar-bam'ik). カルバモイルカルバミン酸. = allophanic acid.

***N*-car·bam·o·yl·glu·tam·ic ac·id** (kar'bă-mō-il-glū-tam'ik). *N*-カルバモイルグルタミン酸; $HOOC(CH_2)_2CH(NHCONH_2)COOH$ (尿素サイクルにおいてオルニチンからシトルリンへのカルバモイル化の中間産物. *N*-アセチルグルタミン酸塩合成酵素欠損患者の治療に用いられる).

car·bam·o·yl phos·phate カルバモイルリン酸; $H_2NCO-OPO_3^{2-}$ (カルバモイル基(H_2NCO-)を他の受容体分子に転移することのできる活性中間体. 尿素サイクルでは, オルニチンからシトルリンを生成し, ピリミジン環形成では, アスパラギン酸からウレイドコハク酸を生成する).

c. p. synthetase カルバモイルリン酸シンテターゼ (カルバモイルリン酸の生成を触媒するホスホトランスフェラーゼ. 2 つの重要なアイソザイムが存在する. カルバモイルリン酸シンテターゼ I はミトコンドリア内酵素で, 2ATP, NH_3, CO_2 および H_2O よりカルバモイルリン酸を合成する反応を触媒する. *N*-アセチルグルタミン酸や尿素合成系(尿素回路)の中間体によって活性化される. カルバモイルリン酸シンテターゼ I の欠損により高アンモニア血症になる. カルバモイルリン酸シンテターゼ II は細胞質内酵素で, 生理条件下, NH_3 の代わりに L-グルタミンを窒素源とする(L-グルタミン酸生成). *N*-アセチルグルタミン酸では活性化されない. ピリミジンの生合成経路で見出される).

car·bam·o·yl·trans·fer·as·es (kar'bă-mō-il-trans'fer-ās-ēz) [EC group 2.1.3]. カルバモイルトランスフェラーゼ (1つの化合物から他の化合物へ, カルバモイル基を転移する酵素の総称(例えば, アスパルテートカルバモイルトランスフェラーゼ, オルニチンカルバモイルトランスフェラーゼ)). = transcarbamoylases.

car·bam·o·yl·u·rea (kar'bă-mō-il-yū-rē'ă). カルバモイル尿素. = biuret.

car·ba·myl (kar'bă-mil). carbamoyl の旧つづり.

car·ba·myl·a·tion (kar'bă-mil-ā'shŭn). carbamoylation の旧つづり.

carb·an·i·on (karb-an'ī-on). カルバニオン (陰電荷が炭素原子上にある有機アニオン. 親化合物の名称に -ide(イド), -diide(ジイド)を加えて特定な名称をつける. 例えば methanide (CH_3^-)).

car·bar·il (car-bar-il'). カルバリル. = carbamate.

car·bar·sone (kar-bar'sōn). カルバルソン; 4-ureidobenzenearsonic acid; *N*-carbamoylarsanilic acid (殺アメーバ薬).

car·bar·yl (kar'bă-ril). カルバリル (接触性の殺虫薬. シラミやその他の外部寄生虫撲滅薬. ヒトに毒性を示し, 悪心, 嘔吐, 下痢, 気管支収縮, 霧視, 唾液分泌過剰, 筋攣縮, チアノーゼ, 痙攣, 昏睡, 呼吸不全などを誘発する).

car·ba·zides (kar'bă-zīdz). カルバジド; 1,3-diaminoureas; RNH-NHCONH-NHR'. = carbohydrazides.

car·baz·o·chrome sa·lic·y·late (kar-baz'ō-krōm). サリチル酸カルバゾクロム; adrenochrome monosemicarbazone-sodium salicylate complex (毛細血管透過性の増大に伴う毛細血管出血の全身制御に用いるエピネフリンの酸化生成物).

car·ba·zole (kar'bă-zōl). カルバゾール (炭水化物(ウロン酸, デオキシペントースを含む)と反応し, 糖の種類によって特有の色を呈する色素中間体として炭水化物やホルムアルデヒドの測定や分析に用いる. 紫外線に感光する). = 9-azafluorene; diphenylenimine.

carb·a·zot·ic ac·id (kar-bă-zot'ik). カルバゾチン酸. = picric acid.

car·ben·i·cil·lin di·so·di·um (kar-ben-i-sil'in). カルベニシリン二ナトリウム (6-(α-carboxy-α-phenylacetamido)-penicillanic acid (α-carboxybenzylpenicillin) の二ナトリウム塩. 広範囲のグラム陽性菌および陰性菌に対して有効な半合成ペニシリン).

car·be·ni·um (kar-bēn'ē-ŭm). →carbonium.

car·ben·ox·o·lone di·so·di·um (kar-ben-oks'ŏ-lōn dī-sō'dē-ŭm). カルベノキソロンニナトリウム; 3β-hydroxy-11-oxoolean-12-en-30-oic hydrogen succinate disodium salt (消化性潰瘍の治療に抗炎症薬として用いる糖質コルチコイド).

car·be·ta·pen·tane cit·rate (kar'be-tă-pen'tān). クエン酸カルベタペンタン; 2-(diethylaminoethoxy)ethyl 1-phenylcyclopentyl-1-carboxylate citrate (アトロピン様作用, 局所麻酔作用を有し, 上気道感染による急性の咳を鎮めるのに効果的である).

carb·he·mo·glo·bin (karb'hē-mō-glō'bin). = carbaminohemoglobin.

car·bide (kar'bid). カーバイド, 炭化物 (炭素より電気的陽性の強い元素を有する炭素化合物. 例えば炭化カルシウム CaC_2).

car·bi·do·pa (kar-bi-dō'pă). カルビドパ; α-methyldopahydrazine; (−)-L-α-hydrazino-3,4-dihydroxy-α-methylhydrocinnamic monohydrate (脳に移行しないドパ脱炭酸酵素阻害薬で, パーキンソン病の治療においてL-ドパの投与量を減らし, 副作用を軽減するためにレボドパと併用される).

car·bi·ma·zole (kar-bī'mă-zōl). カルビマゾール; 1-methyl-2-imidazolethiol ethyl carbonate (甲状腺機能亢進症の治療に用いる).

car·bi·nol (kar'bi-nol). カルビノール. = *methyl* alcohol.

car·bi·nox·a·mine ma·le·ate (kar-bi-nok'să-mēn). マレイン酸カルビノキサミン; paracarbinoxamine maleate; 2-[*p*-chloro-α-(2-dimethylaminoethoxy)benzyl]pyridine maleate (抗ヒスタミン薬).

car·bo [L. coal]. = charcoal.

carbo- →carb-.

car·bo·ben·zoxy (Z, Cbz) (kar'bō-ben-zok'sē). カルボベンゾキシ. = benzyloxycarbonyl.

car·bo·cat·i·on (kar-bō-kat'ī-on). →carbonium.

car·bo·he·mo·glo·bin (kar'bō-hē-mō-glō'bin). カルボヘモグロビン, カルボ血色素. = carbaminohemoglobin.

car·bo·hy·drates (kar-bō-hī'drāts). 炭水化物. 含水炭素.

carbamate (kar′bă-māt)

1. A salt or ester of carbamic acid forming the basis of urethane hypnotics.
2. A group of cholinesterase-inhibiting insecticides resembling organophosphates; the most frequent carbamate is carbaril.

Syn: carbamoate, carbaril

Prev

carbamoyl (kar′bă-mō-il)

The acyl radical, NH_2—CO—, the transfer of which plays an important role in certain biochemical reactions; *e.g.*, in the urea cycle, via carbamoyl phosphate.

Prev

Document 1

Increasing activity of the compound of Reference Example 15 on bladder contraction

Experimental Method

Action of ChE inhibitor on isolated detrusor muscle preparation

i) Preparation of detrusor muscle preparation

5 Week old Hartley male guinea pigs weighing 270-360 g (Japan SLC) were used. After sacrifice of the animal by decapitation, the bladder was extirpated, and muscle slices of about 10mm long and about 4mm across were prepared in a longitudinal direction from the portion except bladder trigone.

ii) Measurement of tone

The contraction tone was measured with an isometric strain transducer (UL-10GR, Nippon Koden and TSD125C, Biopac systems), and the data was collected on a personal computer with a frequency of 5 samples/second through amplifier (BP1257, Sanei, Tokyo and DA100C, Biopac systems) and multichannel data analyzer (MP100A-CE, Biopac systems), and was analyzed by means of purpose-made software

(Acqknowledge 3.5.3, Biopac Systems). In Magnus bath filled with Krebs solution which was bubbled with 95%O_2+5%CO_2 (120.7mmol/L NaCl, 5.9mM KCl, 15.5mmol/L $NaHCO_3$, 1.2mmol/L NaH_2PO_4, 2.5mmol/L $CaCl_2$, 1.2mmol/L $MgCl_2$, 11.5mmol/L D-glucose), a muscle slice was suspended with a load of about 1 g. After equilibrium time of 30 minutes or more, depolarizing contraction was induced with 100mmol/L KCl-Krebs solution (26.6mmol/L NaCl, 100mmol/L KCl, 15.5mmol/L $NaHCO_3$, 1.2mmol/L NaH_2PO_4, 2.5mmol/L $CaCl_2$, 1.2mmol/L $MgCl_2$, 11.5mmol/L D-glucose). Hereinafter, each measurement was performed according to the following method.

iii) Nicotine-induced contraction

After equilibrium time of 30 minutes or more, nicotine of 1-1000 μmol/L was treated, and concentration-dependent curve of the contraction was prepared. Each isolated detrusor muscle was treated with one concentration of nicotine. Nicotine was dissolved in Krebs solution.

iv) Action of ChE inhibitor

After equilibrium time of 30 minutes or more, each kind of ChE inhibitors was treated for 30 minutes, and then nicotine (100 μmol/L) was treated. Atropine (1 μmol/L) was treated 30 minutes before treatment with ChE inhibitor or at the same time, and further the tone was observed for 30 minutes. Atropine was dissolved in Krebs solution and ChE inhibitor was dissolved in distilled water.

v) Data analysis

The mean value of tones for 30 seconds right before treatment with 100mmol/L KCl or nicotine was made a basal value, and the value after subtracting the basal value from the maximum value after treatment was made the contraction tone. The action of drugs on the basal tone was studied by calculating the mean value of tones before drug-treatment and for a duration of 30 seconds at 30 minutes after the treatment. The change of contraction tone by drugs was normalized as a contraction tone by 100mmol/L KCl. The comparison between the ChE inhibitor-treated group and the vehicle-treated group was analyzed statistically with Dunnett's test, the difference between presence and absence of atropine-treatment was analyzed statistically with Student's t-test, and the effect of concomitant treatment was analyzed statistically with two-way analysis of variance.

Drugs

The compound of Reference Example 15 and distigmine bromide were synthesized by Takeda Pharmaceutical Company, LTD. Neostigmine bromide, pyridostigmine bromide, tetraisopropyl pyrophosphoramide (iso-OMPA) and (-)-nicotine were purchased from Sigma, bethanechol chloride was purchased from RBI (Natick, MA, USA), atropine sulfate

monohydrate was purchased from Wako Pure Chemical Industries, and urethane was purchased from Aldrich (Milwaukee, WI, USA).

Result

The used 4 ChE inhibitors increased the nicotine-induced contraction reaction of the isolated detrusor muscle preparation concentration-dependently within the range of concentration studied (Fig. 7 and 8). On the other hand, the action on the basal tone was different depending on drugs. Neostigmine and pyridostigmine showed a remarkable facilitation of automatic movement of detrusor muscle and increase in the basal tone after the treatment (Fig. 7). The increasing action in the basal tone of both drugs was concentration-dependent and significant at the same range as the concentration which increased the nicotine-induced contraction (Fig. 8). This action of distigmine was slight, and the compound of Reference Example 15 had no effect on the basal tone.

In addition, in the following Figures 7-11, the term 'Reference Example 15' means the compound of Reference Example 15 of the present application.

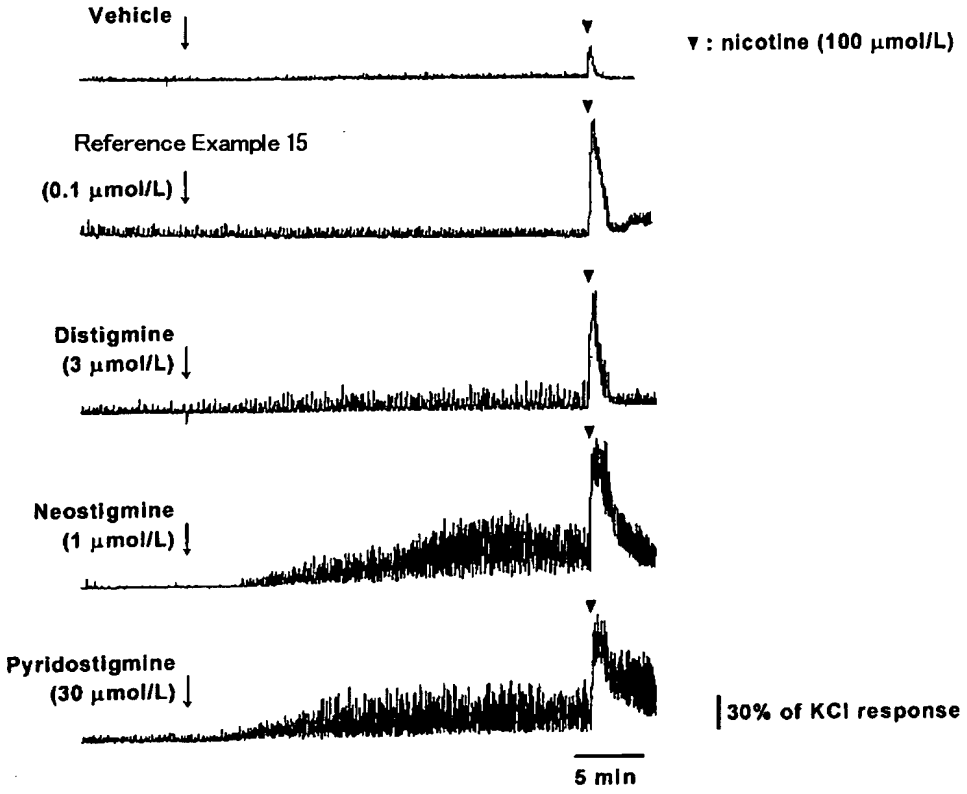
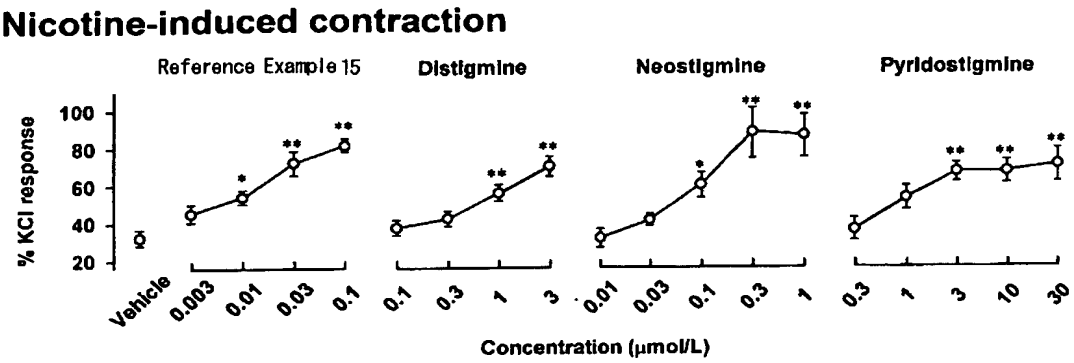


Fig. 7. Typical tracings representing the effects of Reference Example 15 and carbamate AChE inhibitors on the tone of detrusor muscle strips of the guinea pig. The vertical bar and arrowheads indicate 30% of the maximum response induced by 100 mmol/L of KCl-Krebs solution and application of nicotine (100 μmol/L), respectively. Nicotine was applied 30 min after treatment with AChE inhibitors.

A



B

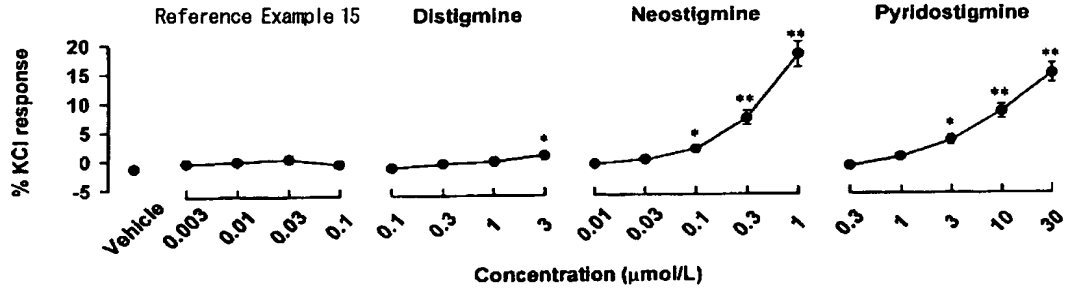


Fig. 8. Effects of AChE inhibitors on the nicotine-induced contractions (A) and basal tone (B) of isolated detrusor muscle of the guinea pig. The ordinates show the values normalized as a % of the KCl-induced contraction. Each value represents the mean ± S.E.M. of eight observations. *P<0.05, **P<0.01 vs. the vehicle-treated group (Dunnett's test).

iso-OMPA alone did not act on the basal tone of the isolated detrusor muscle preparation. However, in the presence of the compound of Reference Example 15 (0.1 μmol/L), facilitation of automatic movement of detrusor muscle was observed and the basal tone was increased concentration-dependently (Fig. 9, 10). The interaction between the two drugs was significant statistically ($p<0.01$, two-way analysis of variance). The increasing activity in basal tone which was observed in the concomitant treatment with the compound of Reference Example 15 (0.1 μmol/L) and iso-OMPA (100 μmol/L) was weaker than that in the treatment only with neostigmine or pyridostigmine.

The increasing activity in basal tone by treatment only with neostigmine or pyridostigmine or by concomitant treatment with iso-OMPA and the compound of Reference Example 15 was completely vanished by atropine (Fig. 11).

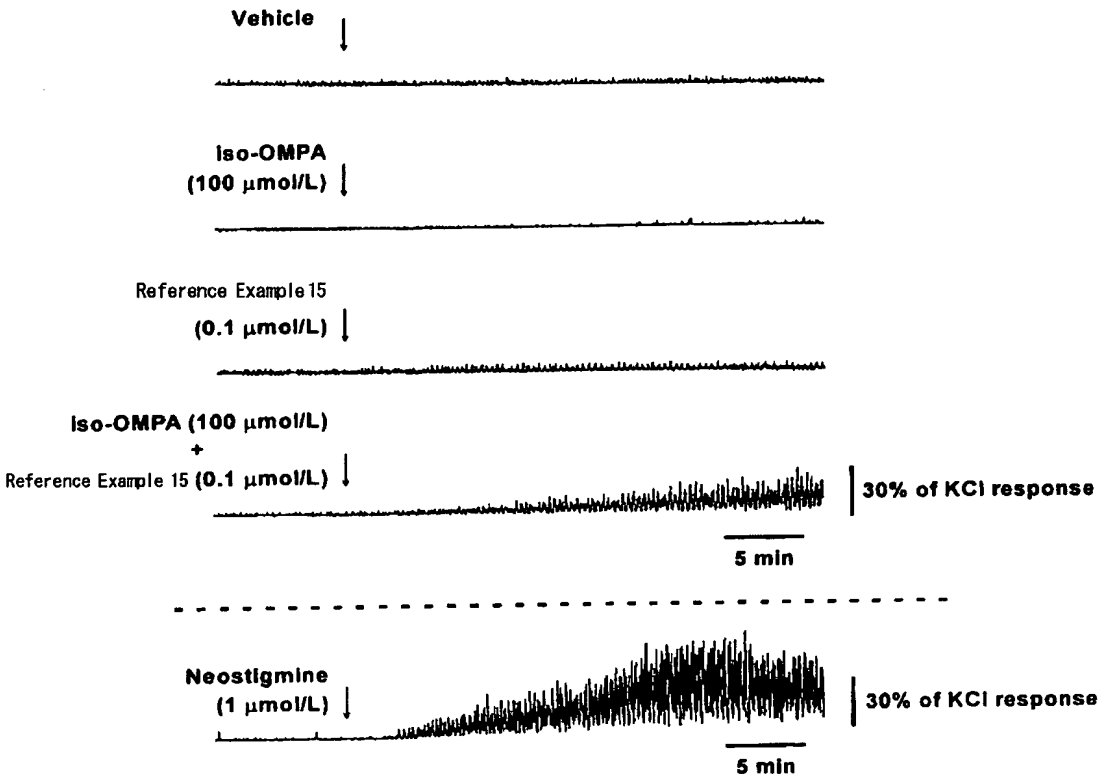


Fig. 9. Typical tracings representing the effects of iso-OMPA, Reference Example 15 and their concomitant treatment on the basal tone of detrusor muscle strips of the guinea pig. A tracing showing the effect of neostigmine are also represented. The vertical bar indicates 30% of the maximum response induced by 100 mM of KCl-Krebs solution.

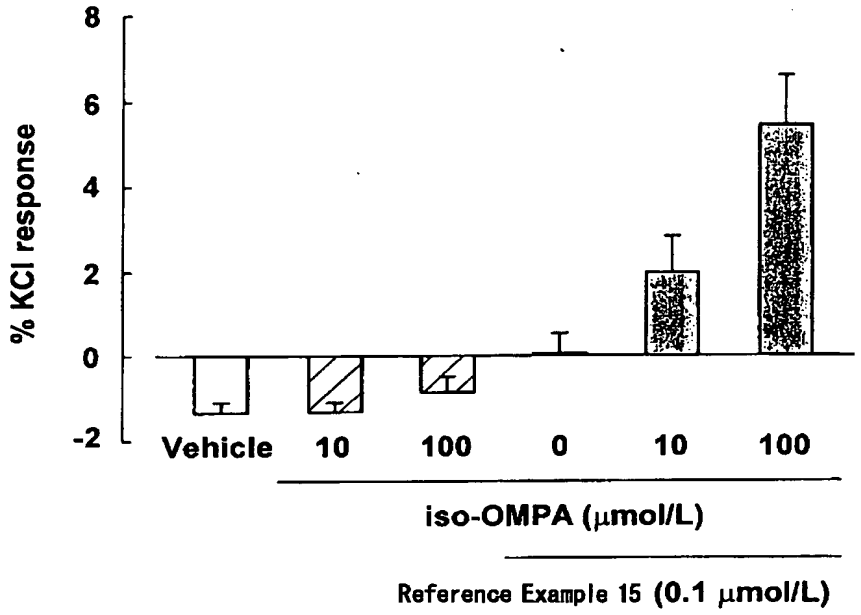


Fig. 10. Effect of concomitant Reference Example 15 and iso-OMPA treatment on the basal tone of detrusor muscle strips. The ordinate shows the values normalized as a % of the KCl-induced contraction. The number under each column indicates the concentration of iso-OMPA (μmol/L). Each value represents the mean ± S.E.M. of eight observations. The concentration of iso-OMPA ($P<0.01$), the co-treatment ($P<0.01$) and, as well as the interaction between the two drugs ($P<0.01$) were all found to be significant by two-way analysis of variance.

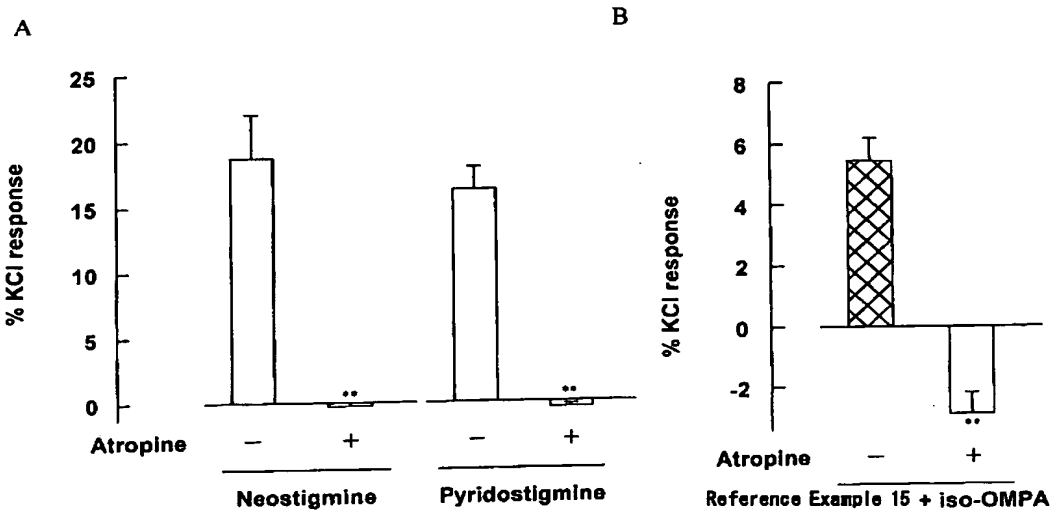


Fig. 11. Effect of atropine on the elevated basal tone of detrusor muscle strips. Atropine (1 μmol/L) completely blocked the increases in the basal tone of the guinea pig detrusor muscle preparations induced by pyridostigmine (30 μmol/L) and neostigmine (1 μmol/L) (A) or co-treatment with iso-OMPA (100 μmol/L) and Reference Example 15(0.1 μmol/L) (B). The ordinate shows the results as a % of the KCl-induced contraction. Each vertical bar represents the mean ± S.E.M. of six observations. **P<0.01 vs. the respective atropine-non-treated group (Student's t-test).

Document 2

Action on urodynamics of the compound of Reference Example 15

Experimental Method

PFS using guinea pigs

i) Animal

5 Week old Hartley male guinea pigs weighing 250-380 g were used.

ii) PFS

Hartley male guinea pigs were anesthetized with urethane (1.5 g/kg, i.p.), and incised at the midline of lower abdomen to expose the bladder. Two injection needles (20G) linked to a polyethylene tube (PE-100, Becton Dickinson) was inserted into the bladder. One of the needles was used for infusion of physiological saline, and the other was used for the measurement of internal pressure of the bladder. Saline was infused continuously at a flow rate of 18 mL/h using a syringe pump (SP-100S, JMS, Tokyo). The infusion was stopped at the time when intermittent urination was confirmed. The saline in bladder was removed by suction. Again, infusion was started, and stopped at the time when a rise of the pressure in bladder was confirmed

immediately before urination. The weight of excreted urine was measured with an electronic force balance (HX-400, A&D, Tokyo), and the internal pressure of the bladder was measured with pressure transducer (TP-400T, Nippon Koden). Analogue data of urine weight and the internal pressure of the bladder were input in a multichannel data analyzer (MP100A-CE, Biopac systems), and was analyzed by means of personal computer and purpose-made software (Acqknowledge 3.5.3, Biopac Systems). Sampling interval of the data was fixed at 0.1 second. In order to remove data noise of the excretion volume and flow rate of urine, the data was adapted to a low pass filter at 0.5Hz. Delay time of 0.1 second at weighing urine was amended, and the value of urine weight was differentiated to determine the flow rate of urine. Measurement was made 2 times before administration of the drug, and then the drug was administered intravenously. The physiological saline in bladder was withdrawn 10 minutes after administration of the compound of Reference Example 15, bethanechol or neostigmine, or 30 minutes after administration of distigmine, and infusion was started again to measure. For the dosage of ChE inhibitor, 3 doses were set centering around MED which increases isovolumic contraction of bladder. The drug was dissolved in distilled water to make the administration volume 0.5 mL/kg. In the present

experiment, the following urodynamic parameters were measured (Fig. 15); bladder capacity, voided volume, maximum intravesical pressure: Pves max, maximum flow rate: Qmax, intravesical pressure at Qmax: Pves(Qmax), urination time, average flow rate: Qave = voided volume/urination time, bladder compliance. The intersection point (volume threshold, pressure threshold) was obtained from the regression lines for the respective intravesical pressure curves of during urinary storage period and on micturition reflex, and the bladder compliance was calculated from the formula of volume threshold/pressure threshold (Fig. 16).

iii) Data analysis

The rate of change before and after the drug administration was calculated for respective parameters, and applied to the Dunnett's test for a significant difference test with the vehicle-administered group. In addition, the difference of Qmax and Pves between the ante-administration and the post-administration was calculated to carry out the pressure/flow rate: P/Q plot analysis.

Drugs

The compound of Reference Example 15 and distigmine bromide were synthesized by Takeda Pharmaceutical Company, LTD. Neostigmine bromide was purchased from Sigma, bethanechol chloride and neostigmine bromide were purchased

from RBI, d-tubocurarine chloride was purchased from Yoshitomi Pharmaceutical Industries, and urethane was purchased from Aldrich.

Result

1) Action on urodynamics of guinea pig

The pre-administration values of various urodynamic parameters in the vehicle-treated group (10 samples) are shown in Table 3.

In addition, in the following Tables and Figures, the term 'Reference Example 15' means the compound of Reference Example 15 of the present application.

Table 3. Pre-administration values of various urodynamic parameters in the vehicle-treated group in the Reference Example 15 -administration experiment

Parameter (unit)	Value	Parameter (unit)	Value
Bladder capacity (mL)	2.00 ± 0.12	Pves(Qmax) (cmH_2O)	21.26 ± 0.73
Voided volume (mL)	1.18 ± 0.11	Average flow rate (mL/s)	0.13 ± 0.02
Pves max (cmH_2O)	26.83 ± 0.91	Bladder compliance (mL/cmH_2O)	0.47 ± 0.05
Qmax (mL/s)	0.20 ± 0.03		

Mean ± S.E.M. N=10.

The changes in urodynamic parameters after

administration of the compound of Reference Example 15, distigmine, neostigmine and bethanechol are shown in Fig. 18 and Table 4. The compound of Reference Example 15 increased significantly the voided volume and Qmax at 0.003 mg/kg, i.v. or more. In this time, influences on Pves max, Pves(Qmax) and the bladder compliance were not observed. Further, significant increases were observed in the bladder capacity at 0.03 mg/kg, i.v., and in Qave at 0.003 and 0.01 mg/kg, i.v.. As for distigmine and neostigmine which are a carbamate ChE inhibitor, similar effects were observed in the change of urodynamic parameters in before and after administration. That is, both drugs did not show an apparent action on the voided volume and Qmax, but increased significantly Pves max and Pves(Qmax). In addition, neostigmine decreased the bladder compliance significantly at 0.03 mg/kg, i.v. or more, and distigmine decreased the bladder compliance significantly at 0.1 mg/kg, i.v.. The effects on bladder capacity and Qave were not observed. Bethanechol decreased significantly the voided volume at 1 mg/kg, i.v. and the bladder compliance at 0.3 mg/kg, i.v. or more. A dose-dependent decrease was observed for the bladder capacity. Effects on other parameters were not observed.

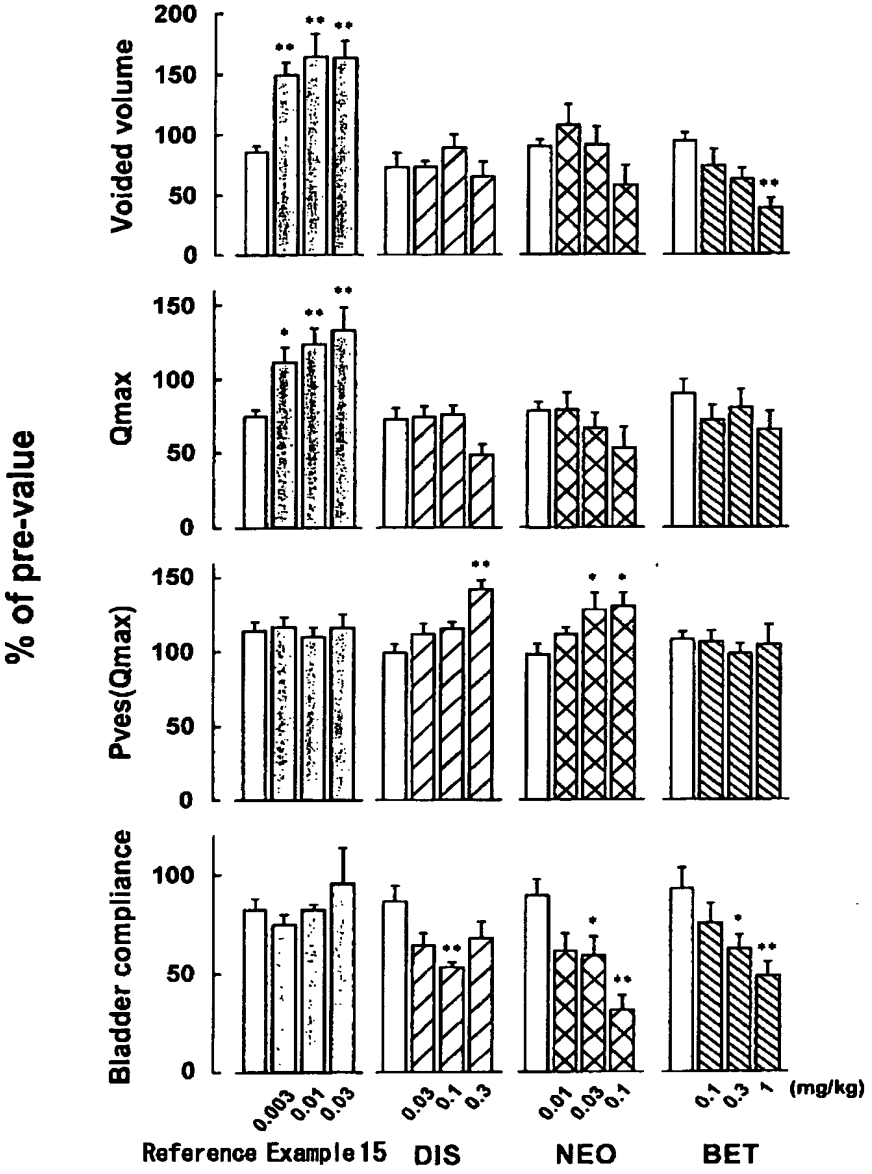


Fig. 18. Changes in various urodynamic parameters after administration of Reference Example 15, distigmine (DIS), neostigmine (NEO) and bethanechol (BET) in guinea pigs. Values are presented as % of the pre-drug values and the mean ± S.E.M. *P<0.05, **P<0.01 vs. vehicle (white column)-treated group (Dunnett's test). N=7-10.

Table 4. Effects of Reference Example 15 and other cholinomimetics on the urodynamic parameters

	Dose (mg/kg, iv)	N	% of pre-value		
			Bladder capacity	Pves max	Average flow rate
Vehicle		10	91.9 ± 3.2	109.3 ± 5.5	77.7 ± 4.4
Reference Example 15	0.003	10	94.6 ± 5.8	118.5 ± 4.8	122.8 ± 11.6 [b]
	0.01	10	101.7 ± 5.0	104.4 ± 5.0	136.0 ± 14.6 [b]
	0.03	10	117.2 ± 9.0 [a]	103.3 ± 5.3	115.5 ± 16.8
Vehicle		10	83.9 ± 5.0	94.1 ± 5.9	68.6 ± 10.8
Distigmine	0.03	10	80.6 ± 3.3	106.8 ± 7.4	63.9 ± 6.9
	0.1	10	83.6 ± 5.9	112.2 ± 6.6	77.9 ± 11.4
	0.3	9	80.0 ± 4.5	145.8 ± 6.6 [b]	47.4 ± 7.7
Vehicle		8	97.2 ± 5.3	101.7 ± 4.4	74.7 ± 8.4
Neostigmine	0.01	7	81.1 ± 8.9	112.2 ± 4.3	82.3 ± 11.7
	0.03	8	86.4 ± 7.5	137.5 ± 17.9 [a]	69.9 ± 15.0
	0.1	8	66.5 ± 14.7	133.1 ± 9.3 [a]	50.6 ± 15.9
Vehicle		8	96.0 ± 4.4	103.5 ± 4.1	84.7 ± 8.5
Bethanechol	0.1	8	86.0 ± 2.5	110.8 ± 7.3	69.3 ± 8.9
	0.3	8	85.3 ± 6.3	98.5 ± 5.0	71.6 ± 11.5
	1	7	66.3 ± 6.0 [b]	111.5 ± 9.5	55.0 ± 13.2

Mean ± S.E.M. a $P<0.05$, b $P<0.01$, vs. vehicle (Dunnett's test).

The result of P/Q plot analysis is shown in Fig. 19. The administration of the compound of Reference Example 15 increased Qmax without affecting Pves(Qmax). On the other

hand, Pves(Qmax) was increased dose-dependently after the administration of distigmine and neostigmine, and a decreasing trend was observed in Qmax. Effects of bethanechol on Pves(Qmax) and Qmax was not observed in every dose used.

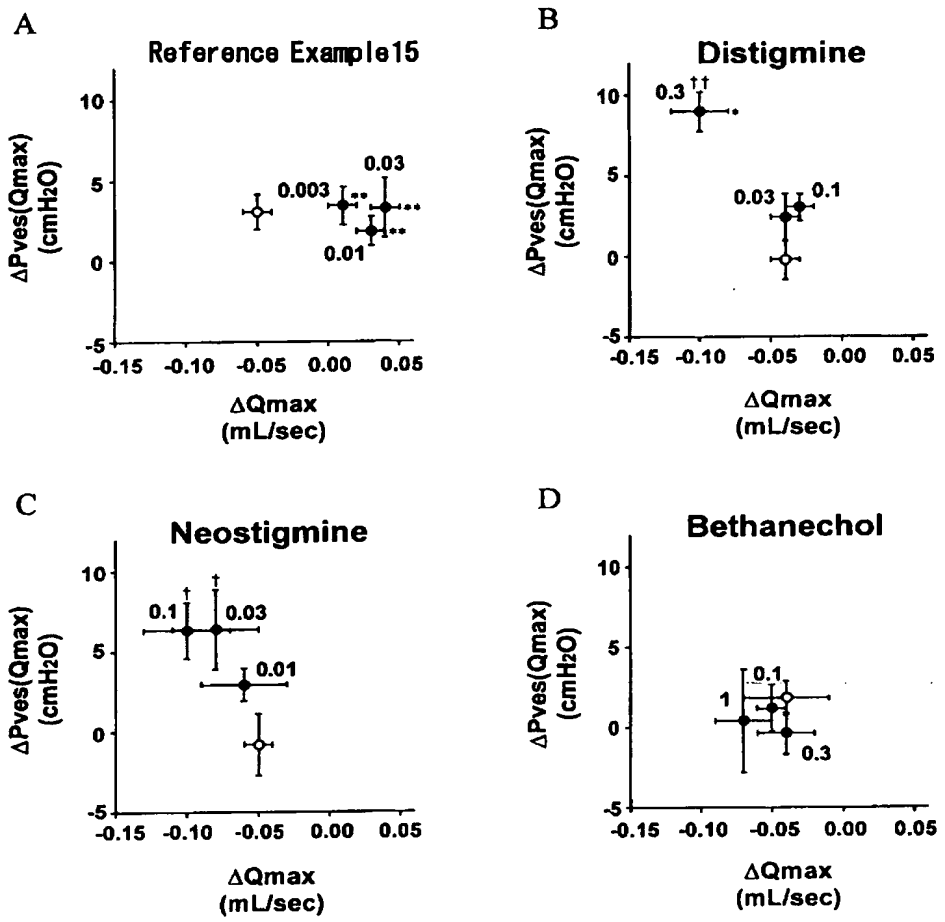


Fig. 19. Effects of Reference Example15(A), distigmine (B), neostigmine (C) and bethanechol (D) on the pressure-flow characteristics in guinea pigs. Values are represented as the differences between the pre-drug and post-drug values, and the mean ± S.E.M. The numbers besides the filled circles indicate dosage (mg/kg, i.v.). The values in the vehicle-treated group are denoted by open circles. *P<0.05, **P<0.01, vs. Δ maximum flow rate in the vehicle-treated group (open circles), †P<0.05, ††P<0.01, vs. Δ intravesical pressure at the maximum flow rate in the vehicle-treated group (Dunnett's test).